Dialogue

S：Sanofi
C：CGU_Taiwan

Research

S: We appreciate that you are working on the adjuvant development. Adjuvants are rather hard for research since it often failed in the begining of clinical trials. Also, adjuvants are a relative profound knowledge, if you go to hospital to ask 100 doctors what an adjuvant is, there is only 1 of them might say he or she understands adjuvants.

S: Why can *Leishmania* trigger so intense immune response; nonetheless, nowadays there are not related anti-Leishmania antibody to fight against the illness *Leishmania* cause?
C: The *Leishmania* we use in our project is double-photo-inactivated one; it consequently had its intact dead body with specific glycoprotein as surface antigens which can be recognized by the antigen presenting cells (APC) in the immune system. However, the general wild-type *Leishmania* hosts in APCs and will repress and escape from immune response, which is the reason the infectious *Leishmania* didn't have its developed commercial antibody.
S: Then you should emphasize that infectious *Leishmania* and immunized *Leishmania* have different roles in order not to make others perplexed.
C: Hence people can know that *Leishmania* will virtually stimulate immune response, meanwhile without being detected in the immune system.

S: What's the advantage of *Leishmania* as an adjuvant?
C: *Leishmania* can effectively trigger immune response. Moreover, it has dual function in humoral and cell-mediated immune response. That means it can potentially induce antibodies production via CD4 T cell activation in humoral pathway,. Aalso intensely stimulate CD8 T cell to undergo cytotoxic pathway. It can provide preventive and therapeutic functions.
S: Yes, besides the APCs recruitment, PRR & inflammasome activation, MHC presentation as the generally essential features of mechanisms that a typical adjuvant can do, you should reveal these unique perspectives.

S: What can we know whether Leishmania is dead or not?
C: We distinguish survival and dead Leishmania by flagella movement, MTT assay,

antibody production in mice.
S: Safety concern is the most important aspect of vaccination that people take, so you need to clearly elucidate this part.
C: Yes. Additionally, the photosensitizers to kill *Leishmania* will accumulate in *Leishmania's* body and will be metabolized in mammalians.
S: Then, will *Leishmania* have an adverse environmental impact?
C: No, it won't. Once *Leishmania* left the medium, it will not successfully survive in different pH or humidity place.
S: But maybe in other countries, there are potentially media for the delivery of *Leishmania*. Also, the vaccine would even be utilized and sold all over the world. Therefore avoid just examining from the standard of Taiwan or Western.

C: If someone judged our dead *Leishmania* for the safety concern, why the general public can accept the live attenuated vaccines in the past?
S: From the commercial view, if current techniques are not advanced enough to develop an inactivated vaccines during outbreak, people have no choice but to accept relatively better live attenuated vaccines. Nowadays, people still inject live attenuated vaccines, such as measles vaccines. Moreover, you need to think about the importance of your Leishmania as an adjuvant, since concentrated antigen can also work efficiently without adjuvants.

Manufacturing
C: How would vaccine be in combination with adjuvant?
S: It is also the question of all pharmaceutical biotech companies. Many factors like surrounding of the factory such as temperature, pH, and moisture, are likely to put influence on it.

C: How the doseage of vaccination be determined?
S: Track the amounts of antibody in the blood routinely and observe the viremia.

S: The cost of incubation of *Leishmania* is high, right?
C: Yes, medium is not cheap on the bench work.
S: And you also speak of the cell-mediated pathway of *Leishmania*.
C: Yes, it has already been proved by scientists.
S: Thereby, *Leishmania* can be used with severe disease vaccines together and enhance its economic value in the long term.
C: What kind of disease vaccines do you suggest?

S: For example, there isn't formal vaccine for hepatitis C; malaria vaccine is not efficient at enhancing the immunologic prevention due to lack of T cells stimulation; tuberculosis vaccine is made of bovine's live attenuated antigen limited to one shot with short maintenance of protection.

Clinical trials

C: How big is the possibility that our project gets approved by the FDA if inactivate *Leishmania* is proven to totally safe?

S: Preclinical trials, animal tests, 3-phrases clinical trials are a long term process acquiring complicated examination and solid, very firm data to support. In accordance with statistics, the successful possibility of whole trials is 1 per million; and that of animal test is 1 per 10 thousand.

C: If got approved by FDA, what is the challenge in foreseeable future?

S: Due to the large gap between bench work and industry, it may require more costs on industrial production. And how adjuvants could be used with vaccines together and what target antigen to choose are also the problems. Look on the dark side, people may have no faith in government and are unwilling to accept it.

S: By the way, what is the probable target protein you want to use?

C: Our project aims to utilize hemagglutinin (HA) in influenza virus. At current stage, we use OVA as a detected tool to confirm our system, because OVA is a commonly used antigen protein to produce the antibody.

Market

C: If any companies will accept technology transfer and commercializing our project if it is workable?

S: If it is safe, effective, and even mere side effects, there must be a lot of companies willing to get the permission, and angel investors will also greatly and automatically invest.

C: Is there a large population of researchers studying in adjuvant?

S: Yes, of course. There are mammothly severe diseases in the world, thus, a potential market indeed exists.

C: How to do a marketing of vaccines?

S: It is really a big question. Generally speaking, targeting specific disease and marketing the demand. What's more the industry will easier to develop vaccines under the support of government authority.

C: From vaccine study to launch, how long will it take empirically?
S: It takes about 12 to 15 years to develop a vaccine. Outcome of vaccine research is always in the two extreme opposites, either no efficacy or severe adverse side effect. And the time needed will inevitably increase as people get to know more and laws of clinical trials get revised more and more strictly.

C: In vaccine industry, what are the most adverse and places?
S: Research and development (R&D) is the most difficult part. Almost easily-manufactured vaccines have been developed. People know the emergency of develop vaccines against disease, however, only in vain ending up limited development.
C: How many years it take to earn the revenue back to make up for the cost on the industry?
S: It depends on your research, manufacturing, patent maintenance, and clinical trials. For example, SANOFI spent NT$15,000,000,000 on just a factory in French for developing and researching dengue vaccine.
S: Vaccine or other associated biotech industry is actually an intensive capitalism game, and the rich can take their chance. It needs to pay their employees and should take the risk of failure; if failed, it is just like to throw the money to the ocean.

C: how many customers are willing to accept vaccine which contains dead parasites?
S: Marketing and thinking of the demand! While developing the vaccines, think of the third world.

C: From the point of supply, what is the most important?
S: It is also its research and development part. The most rapid vaccine is the influenza vaccine with 6 to at most 24 months, because it needs to do quality control constantly to test its efficacy and potency; if something wrong happened to just one of the tests, all are going to be thrown away and required to redo again. Present 5 in 1 or 6 in 1 vaccines are only developed and successful in two companies, GSK7 and SANOFI. Japan has just proceeded to 3 in 1.

C: From the point of demand, what is the most important?
S: It is safe, effective with no side effects and low costs, but currently most vaccines are non-cellular and thus comparatively expensive.

Promotion
C: What is the momentum to promote vaccination?

S: People are not willing to take a vaccine until there is a severe epidemic. It takes lots of effort to ask someone to get vaccinated that the disease is no longer prevalent or is well under control. Accordingly, it may need the public health experts' assistance or promote of vaccination significance on the internet. Regardless, do you know the difference of prevention and treatment?
C: Yes.
S: It would be more acceptable for public to take the therapy if Leishmania can be applied in oncology which provides another chance to have their illness recovered.

Regulation
C: Is there any limit of law or constraint of moral ethics to refrain from the injection of (dead) creatures into body, especially parasitism?
S: Only based on its scientific concept is workable or not and reports of clinical trials